Long-term Clinical Morbidity in Patients With Renal Angiomyolipoma Associated With Tuberous Sclerosis Complex

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OBJECTIVE To estimate the incidence rates of kidney-related clinical outcomes among patients with tuberous sclerosis complex (TSC)-related angiomyolipoma (AML) compared to an age-matched control cohort in the United States.

MATERIALS AND METHODS This was a retrospective, observational study. Administrative data from the MarketScan Research Databases were used to select patients with TSC and renal AML. An age-matched group with no TSC or renal AML was identified for comparison. Outcomes were incidence rates per 100 patient-years and number of months to development of hematuria, chronic kidney disease, renal hemorrhage, kidney failure, and inpatient death.

RESULTS Among the commercially insured TSC-renal AML patients (N = 605) and matched controls (N = 1815), 37.2% were <18 years old. Among Medicaid TSC-renal AML patients (N = 246) and matched controls (N = 738), 38.6% were aged <18. In the commercial sample, in both age groups (<18 and ≥18), the incidence rate of each clinical outcome measured was higher in the TSC-renal AML cohort than in the control cohort, with several differences reaching statistical significance. Compared with younger patients, older TSC-renal AML patients had higher incidence rates of clinical outcomes (hematuria: 20.4 vs 8.7; chronic kidney disease: 9.6 vs 3.5; renal hemorrhage 2.7 vs 0.7; kidney failure: 1.9 vs 0.4) and took less time on average to develop each clinical outcome. A similar pattern of results was observed among patients with Medicaid insurance.

CONCLUSION TSC-renal AML patients are at significantly higher risk for renal morbidity relative to the general population. UROLOGY 95: 80–87, 2016. © 2016 The Authors. Published by Elsevier Inc.

Tuberous sclerosis complex (TSC) is an autosomal dominant syndrome that arises from inactivating mutations in either *TSC1* (chromosome locus 9q34.3) or *TSC2* (chromosome locus 16p13.3), which encode hamartin and tuberin, respectively.[1,2] Aberrant expression of either protein results in benign tumor growth in multiple organ systems, including the brain, kidneys, heart, lungs, eyes, and skin.[3] In the United States, TSC has an estimated incidence of 1 in 6000 live births and affects 25,000-40,000 people; worldwide, 1-2 million people are affected by the disorder.[4] TSC occurs in both children and adults, and shows no gender, racial, or ethnic bias.[5]

TSC commonly affects the central nervous system and results in an array of neuropsychiatric symptoms.[6] Renal manifestations are the second most common and potentially serious presentations of TSC, with incidence rates between 60% and 75%.[7,8] An ultrasound study found that 57.5% of TSC patients between age 1 month and 59 years had renal involvement (eg, angiomyolipomas [AMLs], renal cysts, renal cell carcinoma), with renal cystic disease and renal AMLs, the 2 most common phenotypic expressions of TSC, in the kidney.[2] Both of these renal pathologies cause chronic kidney disease (CKD) and renal failure.[9] In addition, kidney damage due to TSC has an early onset.[10] A

Financial Disclosure: *Judith Prestifilippo and Zhimei Liu are employees of and stockholders at Novartis. John Bissler, John Hulbert, and Hearns Charles were paid consulting fees by Novartis for their contributions to this study. Xue Song, Katherine Cappell, and Christopher Gregory are employees of Truven Health Analytics, which was paid by Novartis to conduct this study and to develop this paper. All authors, including those employed by the study sponsor, participated in the collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication.*

Funding Support: *This study was funded by Novartis Pharmaceuticals Corporation.*

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Submitted: March 22, 2016, accepted (with revisions): April 22, 2016

http://dx.doi.org/10.1016/j.urology.2016.04.027
0090-4295

study of 41 pediatric TSC patients in Italy has seen renal involvement (eg, AMLs, renal cysts, polycystic kidney disease) in 36.6% of them.[11]

Renal AMLs develop in approximately 80% of adults and adolescents with TSC.[12,13] AMLs associated with TSC vary in size, are typically multiple, and located bilaterally in the kidneys.[14] The presence of multiple and bilateral lesions along with the distorted anatomy of renal AMLs makes treatment difficult. The potential complications of AMLs include retroperitoneal hemorrhage, hematuria, renal bleeding, and CKD.[2] AMLs can destroy the adjoining normal renal parenchyma leading to CKD and end-stage renal disease (ESRD).[15,16] ESRD is a significant cause of morbidity and mortality in patients with TSC.[17] A survey from 260 French dialysis centers reported that the approximate prevalence of TSC-associated ESRD was 0.7 case per million and that of ESRD in TSC was 1 per 100.[18] Similarly, another survey carried out in the United Kingdom reported an ESRD prevalence of 1% in TSC patients with normal intellect.[17] Death due to renal complications represents the second most common cause of mortality in patients with TSC and the leading cause of death in adults with TSC.[19] In a US hospital based study of TSC patients, approximately 30% (11 of 40) of deaths directly attributable to TSC were due to renal complication. Of the 11 renal complication deaths reported in the study, 7 were due to renal failure, 2 due to metastatic renal cell carcinoma, and 2 due to bleeding AMLs.[19] Current therapeutic options for treating renal AMLs vary from minimally invasive procedures such as renal arterial branch embolization, to more complex and invasive wedge resection, partial nephrectomy, or radical nephrectomy.[20]

The findings from these studies demonstrate that patients with TSC-related renal AML are at high risk for developing renal complications. However, existing studies are either based on old data or conducted in countries outside the United States. Currently, contemporary estimates of the real-world incidence of kidney-related clinical outcomes in patients with TSC-related AML in the United States are unavailable. Therefore, this retrospective study estimates the incidence rates of kidney-related clinical outcomes (ie, hematuria, renal hemorrhage, CKD, kidney failure, inpatient death) among patients with TSC-related AML in comparison to an age-matched cohort of patients without TSC or renal AML.

MATERIALS AND METHODS

Overview of Study Design

This was a retrospective cohort study based on US administrative insurance claims data for a nonprobability sample of individuals with employer-sponsored commercial health insurance or with Medicaid-sponsored health insurance. Patients diagnosed with TSC and renal AML and a matched cohort of patients without TSC or renal AML were followed up until the earliest of inpatient death, or the end of continuous enrollment, or the end of the study period to measure and compare the presence of kidney-related clinical outcomes.

Data Source

The study data were administrative insurance claims data contained in the *Truven Health MarketScan Commercial Claims and Encounters* (Commercial) and *Multi-State Medicaid* (Medicaid) databases (Truven Health Analytics, Ann Arbor, MI, US). These databases contain enrollment information, inpatient and outpatient medical, and outpatient pharmacy claims data for individuals with employer-sponsored primary health insurance and those with health insurance sponsored by Medicaid programs in multiple states across the United States. The data in these databases are the basis of over 700 peer-reviewed articles published in clinical, health policy, and health economics journals covering a wide range of therapeutic areas.[21-23]

The study databases satisfy the conditions set forth in Sections 164.514 (a)-(b)1ii of the Health Insurance Portability and Accountability Act of 1996 privacy rule regarding the determination and documentation of statistically de-identified data. This study used only de-identified patient records and does not involve the collection, use, or transmittal of individually identifiable data. Institutional Review Board approval to conduct this study was not necessary.

Study variables were measured from the databases using enrollment records, *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) codes, Current Procedural Terminology 4th edition (CPT-4) codes, Healthcare Common Procedure Coding System (HCPCS) codes, and hospital revenue codes, as appropriate.

Patient Selection Criteria

TSC-Renal AML Cohort. The patient selection window was January 1, 2000 to March 31, 2013 for the sample drawn from the Commercial database and January 1, 2000 to June 30, 2012 for the sample drawn from the Medicaid database. Patients were selected into the TSC-renal AML cohort if they met the following criteria: had at least 1 medical claim with a diagnosis of TSC (ICD-9-CM 759.5) during the patient selection window; had evidence of renal AML during the patient selection window as determined using the following ICD-9-CM diagnosis code algorithm applied to medical claims: [223.0]; or [593.81]; or [599.71 and (593.9, 789.35, or 739.36) within 30 days]; or [789.09 and 593.9 within 30 days]; or [789.09 and (789.35 or 789.36) within 30 days] and not [441.3, 441.4, 577.8, 759.0, 789.1, or 789.2]. The *index date* was set as the date of the first TSC or renal AML diagnosis, whichever occurred first, during the patient selection window.

Matched Control Cohort. To create an age- and index-year-matched sample of patients without TSC-AML (controls), the following steps were undertaken separately in the Commercial and Medicaid samples. First, for each TSC-AML patient (cases), 200 potential controls who matched the case in age range during the case's index year were identified (age ranges: <18, 18-34, 35-44, 45-54, 55-64, ≥65 years). Second, from each set of 200 potential age-matched controls, those with any medical claims with a diagnosis of TSC (ICD-9-CM 759.5) or any of the diagnoses used in the renal AML algorithm during the patient selection window were excluded. Third, 3 of the remaining potential matches for each case were randomly selected. Finally, the index date for each of the 3 randomly selected, age-matched, TSC, and renal-AML-free control patients was set to the index date of the corresponding case. The result was a group of age- and index-year-matched control patients with no evidence of TSC or renal

AML during the patient selection period that was matched to the group of TSC-AML patients in the ratio of 3:1.

The study used a variable duration of follow-up, and all patients were followed from the index date until the earliest of inpatient death, the end of continuous health plan enrollment, or the end of the study period. There was no minimum duration of follow-up required for inclusion in the study.

Outcome Measures

Incident clinical outcomes were measured during the variable duration follow-up period. The clinical outcomes measured were hematuria, CKD, renal hemorrhage, kidney failure (defined as evidence of dialysis or kidney transplant), and inpatient death. An outcome was considered incident if it was observed during the follow-up period, but not during all available data prior to the index date. Due to the small sample size, no minimum baseline period was required; therefore the amount of available data prior to the index date was allowed to vary by patient. Evidence of an incident condition was defined as at least 1 medical claim with a diagnosis, procedure, or revenue code for the condition during the follow-up period and no medical claims with codes for the condition during all available data prior to the index date. The codes used to define each clinical condition were available upon request. Inpatient death was identified using the reported patient discharge status on inpatient claims (death outside of the inpatient setting cannot be identified using administrative claims and would have been captured instead as the end of health plan enrollment). The risk of newly developing each of the clinical outcomes was measured over a time period of 100 person-years (eg, a rate of 10 would signify that if we were to follow 100 people for 1 year, we would expect to observe 10 new cases of the outcome). Incident outcome event rate was calculated as the number of patients with outcome divided by sum of days from index date to outcome among patients with outcome + sum of days of follow-up among patients without outcome multiplied by 365 and 100.

Statistical Analyses

Bivariate descriptive analyses were conducted on all study outcomes, stratified by cohort (TSC-renal AML or control). To

Table 1. Demographic characteristics (commercial population)

	Age <18 y			Age ≥18 y		
	TSC-Renal AML N = 225	Control N = 675	*P* Value	TSC-Renal AML N = 380	Control N = 1140	*P* Value
Age (Mean, SD)	9.8 (4.9)	11.2 (4.9)	<.05	36.9 (13.0)	37.0 (14.0)	.9
Age group (N, %)			–			–
<18	225 (100%)	675 (100%)		0 (0.0%)	0 (0.0%)	
18-34	0 (0.0%)	0 (0.0%)		180 (47.4%)	540 (47.4%)	
35-44	0 (0.0%)	0 (0.0%)		81 (21.3%)	243 (21.3%)	
45-54	0 (0.0%)	0 (0.0%)		74 (19.5%)	222 (19.5%)	
55-64	0 (0.0%)	0 (0.0%)		45 (11.8%)	135 (11.8%)	
65+	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Sex (%, N)			.07			<.05
Male	102 (45.3%)	353 (52.3%)		101 (26.6%)	501 (43.9%)	
Female	123 (54.7%)	322 (47.7%)		279 (73.4%)	639 (56.1%)	
Months of follow-up (Mean, SD)	46.4 (35.1)	49.6 (32.4)	.2	36.7 (31.2)	40.6 (30.5)	<.05
Population density (N, %)			<.05			<.05
Urban	186 (82.7%)	532 (78.8%)		296 (77.9%)	851 (74.6%)	
Rural	30 (13.3%)	142 (21.0%)		66 (17.4%)	286 (25.1%)	
Unknown	9 (4.0%)	1 (0.1%)		18 (4.7%)	3 (0.3%)	
Health plan type (N, %)			<.05			<.05
Comprehensive	12 (5.3%)	49 (7.3%)		21 (5.5%)	105 (9.2%)	
HMO	31 (13.8%)	96 (14.2%)		48 (12.6%)	145 (12.7%)	
PPO	136 (60.4%)	276 (40.9%)		242 (63.7%)	502 (44.0%)	
POS	19 (8.4%)	207 (30.7%)		37 (9.7%)	330 (28.9%)	
Other/Unknown	27 (12.0%)	47 (7.0%)		32 (8.4%)	58 (5.1%)	
Year of index date (N, %)			–			–
2000	10 (4.4%)	30 (4.4%)		9 (2.4%)	27 (2.4%)	
2001	6 (2.7%)	18 (2.7%)		6 (1.6%)	18 (1.6%)	
2002	10 (4.4%)	30 (4.4%)		11 (2.9%)	33 (2.9%)	
2003	8 (3.6%)	24 (3.6%)		20 (5.3%)	60 (5.3%)	
2004	23 (10.2%)	69 (10.2%)		22 (5.8%)	66 (5.8%)	
2005	9 (4.0%)	27 (4.0%)		21 (5.5%)	63 (5.5%)	
2006	25 (11.1%)	75 (11.1%)		39 (10.3%)	117 (10.3%)	
2007	14 (6.2%)	42 (6.2%)		31 (8.2%)	93 (8.2%)	
2008	39 (17.3%)	117 (17.3%)		63 (16.6%)	189 (16.6%)	
2009	27 (12.0%)	81 (12.0%)		50 (13.2%)	150 (13.2%)	
2010	20 (8.9%)	60 (8.9%)		37 (9.7%)	111 (9.7%)	
2011	19 (8.4%)	57 (8.4%)		39 (10.3%)	117 (10.3%)	
2012	13 (5.8%)	39 (5.8%)		31 (8.2%)	93 (8.2%)	
2013	2 (0.9%)	6 (0.9%)		1 (0.3%)	3 (0.3%)	

AML, angiomyolipoma; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; SD, standard deviation; TSC, tuberous sclerosis complex.

examine the outcomes for pediatric and adult populations separately, all outcomes were additionally stratified by age on the index date (<18 vs ≥18 years). Continuous measures were summarized as means and standard deviations. Categorical measures were summarized as counts and percentages. Statistical tests of significance for differences in the study outcomes between patients with and without TSC-AML were performed; chi-square tests were used to evaluate the statistical significance of differences for categorical variables. Fisher exact test was used to evaluate the statistical significance for categorical variables with rare events. To evaluate the statistical significance of differences for normally distributed continuous variables, *t* tests were used. *P* values <.05 were considered, a priori, to be statistically significant.

RESULTS

Study Samples

In the commercial sample, a total of 605 patients with TSC-renal AML (cases) were matched to 1815 control patients: 37.2% (cases: N = 225; control: N = 675) were <18 years of age and 62.8% (cases: N = 380; control: N = 1140) were ≥18 years of age. In the Medicaid sample, 246 cases were matched to 738 controls, with 38.6% < 18, and 61.4% ≥ 18 years old.

Because more than half of the study population did not have continuous enrollment for 6 months prior to the index date, baseline clinical characteristics were not examined in this study. The demographic characteristics of each of the study cohorts are shown in Table 1. Commercially insured TSC-renal AML patients were demographically similar to their matched controls with 2 notable exceptions: first, among patients ≥18 years old, a higher proportion of cases were female as compared to the controls (73% vs 56%; *P* <.05). Second, among those aged <18 years, the mean age of the controls was 1.4 years higher than that of the cases (11.2 vs 9.8; *P* <.05). Among commercially insured patients, the follow-up duration of cases was 3.2-3.9 months shorter than that of the controls (age ≥18: 36.7 vs 40.6; age <18: 46.4 vs 49.6). The opposite pattern was observed in Medicaid patients, with the TSC-renal AML patients having approximately twice the duration of follow-

Table 2. Demographic characteristics (medicaid population)

	Age <18 y			Age ≥18 y		
	TSC-Renal AML N = 95	Control N = 285	*P* Value	TSC-Renal AML N = 151	Control N = 453	*P* Value
Age (Mean, SD)	7.7 (5.5)	8.8 (5.0)	.08	36.0 (12.8)	36.1 (13.5)	.9
Age group (N, %)			–			–
<18	95 (100%)	285 (100%)		0 (0.0%)	0 (0.0%)	
18-34	0 (0.0%)	0 (0.0%)		76 (50.3%)	228 (50.3%)	
35-44	0 (0.0%)	0 (0.0%)		40 (26.5%)	120 (26.5%)	
45-54	0 (0.0%)	0 (0.0%)		24 (15.9%)	72 (15.9%)	
55-64	0 (0.0%)	0 (0.0%)		6 (4.0%)	18 (4.0%)	
65+	0 (0.0%)	0 (0.0%)		5 (3.3%)	15 (3.3%)	
Sex (%, N)			.2			<.05
Male	44 (46.3%)	154 (54.0%)		61 (40.4%)	140 (30.9%)	
Female	51 (53.7%)	131 (46.0%)		90 (59.6%)	313 (69.1%)	
Months of follow-up (Mean, SD)	75.7 (42.8)	33.9 (26.2)	<.05	73.5 (40.8)	35.4 (29.8)	<.05
Population density (N, %)			.2			<.05
Urban	74 (77.9%)	239 (83.9%)		113 (74.8%)	384 (84.8%)	
Rural	21 (22.1%)	45 (15.8%)		36 (23.8%)	69 (15.2%)	
Unknown	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Health plan type (N, %)			<.05			<.05
Comprehensive	59 (62.1%)	94 (33.0%)		115 (76.2%)	270 (59.6%)	
HMO	30 (31.6%)	156 (54.7%)		25 (16.6%)	150 (33.1%)	
PPO	0 (0.0%)	0 (0.0%)		0 (0.0%)	1 (0.2%)	
POS	6 (6.3%)	35 (12.3%)		9 (6.0%)	32 (7.1%)	
Other/Unknown	0 (0.0%)	0 (0.0%)		2 (1.3%)	0 (0.0%)	
Year of index date (N, %)			–			–
2000	15 (15.8%)	45 (15.8%)		31 (20.5%)	93 (20.5%)	
2001	5 (5.3%)	15 (5.3%)		11 (7.3%)	33 (7.3%)	
2002	28 (29.5%)	84 (29.5%)		40 (26.5%)	120 (26.5%)	
2003	7 (7.4%)	21 (7.4%)		20 (13.2%)	60 (13.2%)	
2004	6 (6.3%)	18 (6.3%)		17 (11.3%)	51 (11.3%)	
2005	10 (10.5%)	30 (10.5%)		5 (3.3%)	15 (3.3%)	
2006	6 (6.3%)	18 (6.3%)		3 (2.0%)	9 (2.0%)	
2007	3 (3.2%)	9 (3.2%)		2 (1.3%)	6 (1.3%)	
2008	4 (4.2%)	12 (4.2%)		6 (4.0%)	18 (4.0%)	
2009	3 (3.2%)	9 (3.2%)		8 (5.3%)	24 (5.3%)	
2010	4 (4.2%)	12 (4.2%)		7 (4.6%)	21 (4.6%)	
2011	0 (0.0%)	0 (0.0%)		1 (0.7%)	3 (0.7%)	
2012	4 (4.2%)	12 (4.2%)		0 (0.0%)	0 (0.0%)	
2013	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	

Abbreviations as in Table 1.

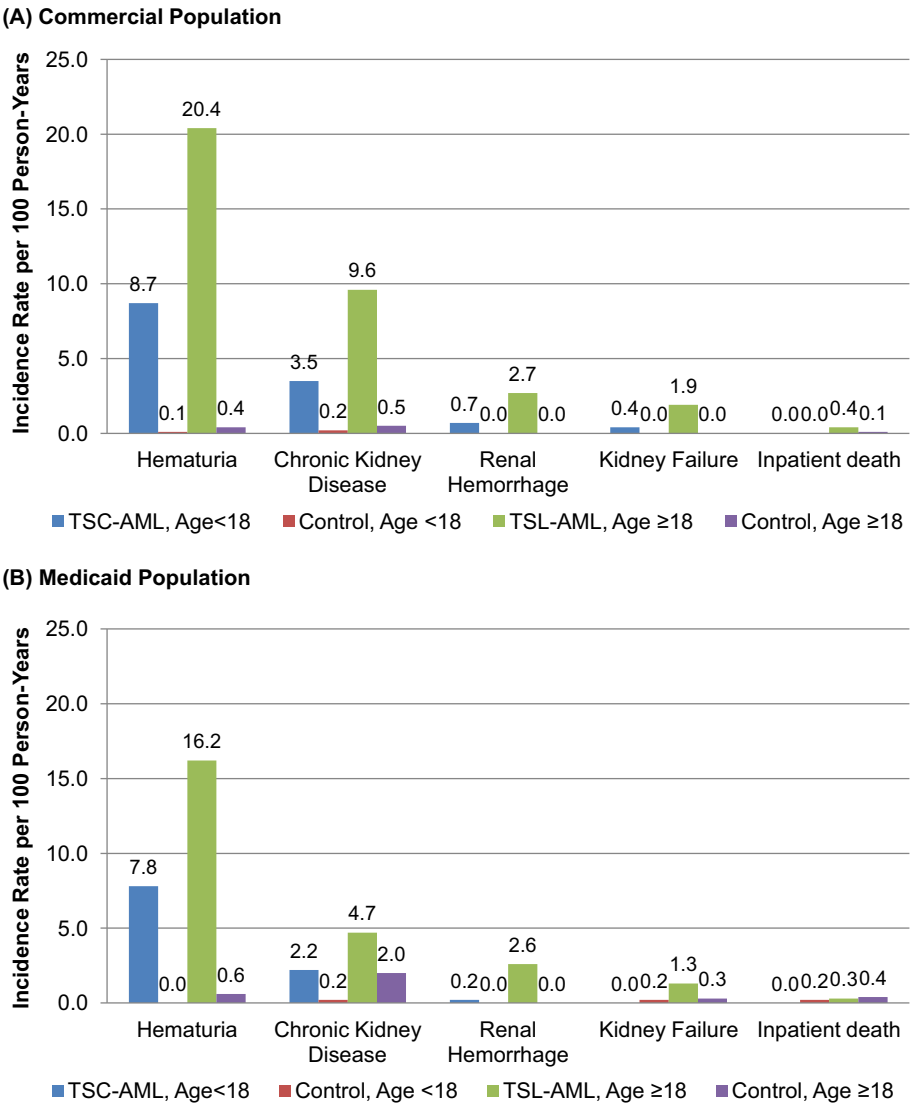

Figure 1. Incidence rates of clinical outcome. (Color version available online.)

up as their matched controls (age ≥18 years: 73.5 vs 35.4; age <18: 75.7 vs 33.9; Table 2).

Clinical Outcomes

Overall, the TSC-renal AML patients had higher incidence rates of the studied negative clinical outcomes than the controls (Fig. 1A,B). Among commercial patients ≥18 years old, the incidence rate per 100 patient-years was significantly higher (P <.05) in the TSC-renal AML cohort than in the control cohort for hematuria (20.4 vs 0.4), CKD (9.6 vs 0.5), and kidney failure (1.9 vs 0). TSC-renal AML patients had a higher incidence rate of inpatient death (0.4 vs 0.1), but the difference was not significant. The incidence rate of renal hemorrhage was also higher for TSC-renal AML patients (2.7 vs 0), but as no control patients developed renal hemorrhage, confidence intervals could not be estimated for this group, and significance inference on renal hemorrhage could not be mathematically performed. The pattern of results was the same in commercially insured patients <18 years old: TSC-renal AML patients had higher incidence rates of clinical outcomes than controls, although the differences were statistically significant for only hematuria and CKD. Among the TSC-renal AML patients, hematuria had the highest incidence rate, followed by CKD, renal hemorrhage, kidney failure, and inpatient death, and the older cohort had higher incidence rates than the younger cohort.

TSC-renal AML patients not only had higher rates of clinical outcomes, but it took them less time to develop such outcomes (Tables 3 and 4). Among commercially insured patients ≥18 years of age, compared to the control cohort, TSC-renal AML patients took much less time for the development of hematuria (13.6 vs 47.5 months; P <.05), CKD (15.1 vs 26.2 months; P <.05), kidney failure (20.1 vs 57.3 months; P <.05), and inpatient death (27.8 months vs 70.4 months; P <.05). In patients <18 years of age, the average time for the development of kidney-related clinical outcomes did not differ significantly between

Table 3. Clinical outcomes (commercial population)

Measure	Age <18 y			Age ≥18 y		
	TSC-Renal AML N = 225	Control N = 675	*P* Value	TSC-Renal AML N = 380	Control N = 1140	*P* Value
Patients with hematuria (N, %)	61 (27.1%)	2 (0.3%)	<.05	152 (40.0%)	13 (1.1%)	<.05
Months to hematuria (Mean, SD)	28.7 (24.8)	24.4 (25.8)	.8	13.6 (17.5)	47.5 (32.2)	<.05
Patients with chronic kidney disease (N, %)	28 (12.4%)	6 (0.9%)	<.05	89 (23.4%)	18 (1.6%)	<.05
Months to chronic kidney disease (Mean, SD)	32.2 (35.0)	42.1 (22.1)	.5	15.1 (18.9)	26.2 (21.4)	<.05
Patients with renal hemorrhage (N, %)	6 (2.7%)	0 (0.0%)	<005	28 (7.4%)	0 (0.0%)	<.05
Months to renal hemorrhage (Mean, SD)	53.4 (52.3)	–	–	9.4 (15.0)	–	–
Patients with kidney failure (N, %)	3 (1.3%)	0 (0.0%)	<.05	20 (5.3%)	1 (0.1%)	<.05
Months to kidney failure (Mean, SD)	40.9 (60.7)	–	–	20.1 (16.6)	57.3 (–)	<.05
Patients with inpatient death (N, %)	0 (0.0%)	0 (0.0%)	–	4 (1.1%)	2 (0.2%)	<.05
Months to inpatient death (Mean, SD)	–	–	–	27.8 (22.1)	70.4 (41.3)	.2

Abbreviations as in Table 1.

Table 4. Clinical outcomes (medicaid population)

Measure	Age <18 y			Age ≥18 y		
	TSC-Renal AML N = 95	Control N = 285	*P* Value	TSC-Renal AML N = 151	Control N = 453	*P* Value
Patients with hematuria (N, %)	37 (38.9%)	0 (0.0%)	<.05	89 (58.9%)	6 (1.3%)	<.05
Months to hematuria (Mean, SD)	50.1 (36.3)	–	–	32.0 (30.2)	21.7 (21.9)	.4
Patients with chronic kidney disease (N, %)	12 (12.6%)	1 (0.4%)	<.05	37 (24.5%)	21 (4.6%)	<.05
Months to chronic kidney disease (Mean, SD)	70.4 (40.1)	6.4 (–)	<.05	44.6 (37.6)	29.6 (18.7)	.09
Patients with renal hemorrhage (N, %)	1 (1.1%)	0 (0.0%)	.08	21 (13.9%)	0 (0.0%)	<.05
Months to renal hemorrhage (Mean, SD)	99.9 (–)	–	–	28.8 (29.9)	–	–
Patients with kidney failure (N, %)	0 (0.0%)	1 (0.4%)	.3	11 (7.3%)	3 (0.7%)	<.05
Months to kidney failure (Mean, SD)	–	11.2 (–)	–	42.1 (45.5)	42.5 (25.9)	.9
Patients with inpatient death (N, %)	0 (0.0%)	1 (0.4%)	.3	3 (2.0%)	4 (0.9%)	.3
Months to inpatient death (Mean, SD)	–	88.7 (–)	–	120.2 (5.5)	35.5 (21.8)	<.05

Abbreviations as in Table 1.

cases and controls. Finally, on average, it took younger TSC-renal AML patients more time to develop each of the clinical outcomes than their older counterparts.

Medicaid patients with TSC-renal AML also had higher incidence rates of hematuria, CKD, renal hemorrhage, and kidney failure than their matched controls (Fig. 1B), although significant only for hematuria and CKD. Additionally, although TSC renal-AML patients in the Medicaid cohort had nearly twice the average duration of follow-up as patients in the commercial cohort, the incidence rates for all clinical outcomes were nominally lower in the Medicaid cohort. The difference between payers was not significant except for CKD.

DISCUSSION

This retrospective cohort study compared the real-world incidence rates of kidney-related clinical outcomes in individuals with TSC-renal AML to those in an age-matched control cohort. Not surprisingly, the incidence rates of hematuria, CKD, kidney failure, and inpatient death were significantly higher in patients with TSC-renal AML than in patients without TSC or renal AML, and older TSC-renal AML patients had higher rates than their younger counterparts. To our knowledge, other contemporary estimates of the rates of kidney-related clinical outcomes in patients with TSC-renal AML in the United States are unavailable. Additionally, we know of no other studies that

have directly compared the rates of these outcomes in TSC renal-AML patients to those in the general population.

Preservation of renal function and prevention of renal complications, such as potentially life-threatening hemorrhage, are the major goals of treating patients with TSC-related AMLs. The guidelines recommend regular renal imaging every 1-3 years for patients with TSC to monitor the presence or progression of renal morbidity,[24,25] although the recommended modality and frequency of imaging varies across the literature.[10,26] Management of AMLs is determined by lesion size and symptoms. Symptomatic AMLs or those greater than 4-8 cm in diameter have been typically managed via embolization, partial nephrectomy, or complete nephrectomy.[10,26-28] Recently, pharmacologic management of renal AMLs with an mTOR inhibitor has become an additional treatment option for patients with TSC.[16,26,29,30] In fact, pharmacologic therapy has become the recommended first-line therapy for AMLs larger than 3 cm, especially if they are growing.[25] It is interesting that in the commercial study population, the proportion of females was much higher among those ≥18 years than among those <18 years (73% vs 55%), whereas in the whole commercial claims database, the proportion of females was similar between the 2 age cohorts (52% vs 49%). This suggests a gender bias toward female in older TSC-AML patients, which may indicate the influence of hormonal differences in women. Future research using other data sources on gender distribution is needed to confirm this observation.

This study had several limitations. First, TSC, renal AML, and clinical outcomes were identified using ICD-9-CM diagnosis or procedure codes, which are subject to miscoding. Second, because more than half of the study population would have been excluded if a 6-month baseline period of continuous enrollment were required, clinical characteristics were not reported for the study population. In addition, patients with incident clinical outcomes were required to have no such clinical conditions during the baseline, but the length of baseline varied across patients. For those with a very short baseline period, incident clinical outcomes may be overestimated. Third, the rate of clinical outcomes is likely to be underestimated due to the relatively short follow-up period. In particular, patients with commercial insurance were followed for approximately 3-4 years on average, and those with Medicaid had approximately 6 years of follow-up. Patients who may have developed the study outcomes after the end of the follow-up period were not captured. Fourth, death was not captured outside of the inpatient setting (and cause of death was unknown), so the death rate was underestimated. Fifth, the sample size of patients with renal AML associated with TSC was very small, thus results may have been biased by outliers. Finally, this study was limited to only those individuals with commercial health coverage or those eligible for Medicaid. Due to the small sample size (12 patients), the Medicare population was not reported. Consequently, results of this analysis may not be generalizable to TSC-AML patients with other insurance or without health insurance coverage.

CONCLUSION

The findings from this study indicate that patients with renal AML associated with TSC are at a significantly higher risk for renal morbidity relative to the general population. Optimal treatment by nephrologists, interventional radiologists, and urologists to anticipate and minimize or prevent the complications associated with this condition is important for long-term maintenance of renal function in patients with TSC-renal AML.

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